International Journal of Infectious Diseases 19 (2014) 26–32

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Prophylactic role of long-term ultra-low-dose acyclovir for varicella zoster virus disease after allogeneic hematopoietic stem cell transplantation

Koji Kawamura, Hidenori Wada, Ryoko Yamasaki, Yuko Ishihara, Kana Sakamoto, Masahiro Ashizawa, Miki Sato, Tomohito Machishima, Kiriko Terasako, Shun-ichi Kimura, Misato Kikuchi, Hideki Nakasone, Rie Yamazaki, Junya Kanda, Shinichi Kako, Aki Tanihara, Junji Nishida, Yoshinobu Kanda *

Division of Hematology, Saitama Medical Center, Jichi Medical University, 1-847, Amanuma-cho, Omiya-ku, Saitama-city, Saitama 330-8503, Japan

ARTICLE INFO

Article history:
Received 28 April 2013
Received in revised form 9 September 2013
Accepted 27 September 2013

Corresponding Editor: Hubert Wong, Vancouver, Canada

Keywords:
Long-term acyclovir
Varicella zoster virus disease
Allogeneic hematopoietic stem cell transplantation
Disseminated VZV disease

SUMMARY

Objectives: To evaluate the prophylactic role of long-term ultra-low-dose acyclovir for varicella zoster virus (VZV) disease after allogeneic hematopoietic stem cell transplantation (HSCT).
Methods: We evaluated 141 patients who were planned to receive acyclovir at 200 mg/day until the end of immunosuppressive therapy and for at least 1 year after HSCT in our center between June 2007 and June 2012.
Results: The cumulative incidence of VZV disease after HSCT was 4.5% at 1 year and 18.3% at 2 years. Protocol violation was the only independent significant factor that increased the incidence of VZV disease (hazard ratio (HR) 7.50, 95% confidence interval (CI) 3.60–15.63). Excluding patients with protocol violation, the discontinuation of acyclovir was the only significant factor for the development of VZV disease (HR 5.90, 95% CI 1.56–22.37). Six patients experienced breakthrough VZV disease, but four of these six had not taken acyclovir for several weeks before breakthrough VZV disease. On the other hand, the cumulative incidence of VZV disease after the cessation of acyclovir was 28.4% at 1 year and 38.0% at 2 years. The proportion of disseminated VZV disease was only 7% and no patient died directly of VZV disease.
Conclusions: This study shows that long-term ultra-low-dose acyclovir appears to be effective for preventing VZV disease, especially disseminated VZV disease, after allogeneic HSCT. We recommend continuing acyclovir until the end of immunosuppressive therapy and for at least 1 year after HSCT, but additional strategies such as the administration of varicella vaccine may be needed to eradicate VZV disease.

1. Introduction

Varicella zoster virus (VZV) disease is a common complication after hematopoietic stem cell transplantation (HSCT), with a relatively high incidence of more than 20%.[1–4] Although a localized dermatomal rash is the major clinical presentation, disseminated VZV disease occasionally occurs and may result in a fatal outcome.[3] In addition, several complications, such as post-herpetic neuralgia and secondary bacterial infections, are occasionally observed,[1,4] and may impair the patient's quality of life. Therefore, to reduce VZV disease and its complications, the long-term administration of acyclovir has been evaluated in several studies.

From the mid-1980s to the mid-2000s, several studies concluded that the overall cumulative incidence of VZV disease was not decreased by prophylactic acyclovir at 600–3200 mg/day for a fixed period of up to 6 months or 1 year, because of the increase in VZV disease after the cessation of long-term acyclovir, although VZV disease was almost completely suppressed during prophylaxis.[5–8] Therefore, the Centers for Disease Control and Prevention/Infectious Diseases Society of America/American Society for Blood and Marrow Transplantation (CDC/IDSA/ASBMT) guidelines of 2000 did not recommend universal long-term acyclovir prophylaxis to prevent VZV disease.[9] However, a large

* Corresponding author. Tel.: +81 48 647 2111; fax: +81 48 644 8167.
E-mail address: ycanda-tky@umin.ac.jp (Y. Kanda).

http://dx.doi.org/10.1016/j.ijid.2013.09.020

retrospective study showed that acyclovir prophylaxis for 1 year reduced VZV disease, which was further decreased by the continuation of prophylaxis in patients who remained on immunosuppressive drugs.[10] Furthermore, we have previously reported that a lower dose of acyclovir at 200–400 mg/day could also reduce VZV disease.[11,12] Another clinical benefit of long-term acyclovir is the reduction of disseminated VZV disease and its complications.[10,12,13] Therefore, long-term acyclovir prophylaxis is routinely recommended for the first year after HSCT in the 2009 guidelines that were co-sponsored by several international groups.[14]

However, the optimal duration of prophylaxis, the minimal effective dose, and the risk factors for VZV disease after cessation remain unclear. In the present study, the clinical courses of patients who were planned to receive acyclovir at 200 mg/day until the end of immunosuppressive therapy and for at least 1 year after HSCT were analyzed retrospectively. First we identified risk factors predictive for the development of VZV disease. In particular, we focused on whether protocol violation was a significant risk factor or not. Next, we assessed the causal effect of acyclovir use/non-use, excluding patients with protocol violation.

2. Patients and methods

2.1. Patients

The clinical charts of 161 consecutive patients who underwent their first allogeneic HSCT between June 2007 and June 2012 at our institution were reviewed retrospectively. Among these patients, 20 were excluded: 14 died within 35 days after HSCT, five failed to achieve complete remission after HSCT, and one experienced graft rejection and early recovery of host-derived hematopoiesis after HSCT. Thus, 141 patients were included in this study (Figure 1). We followed up 102 patients until the last observation (censored observation) or the development of VZV disease, 32 patients until death without VZV disease, and seven patients until second transplantation without VZV disease. The clinical and epidemiological characteristics of the patients are shown in Table 1. This

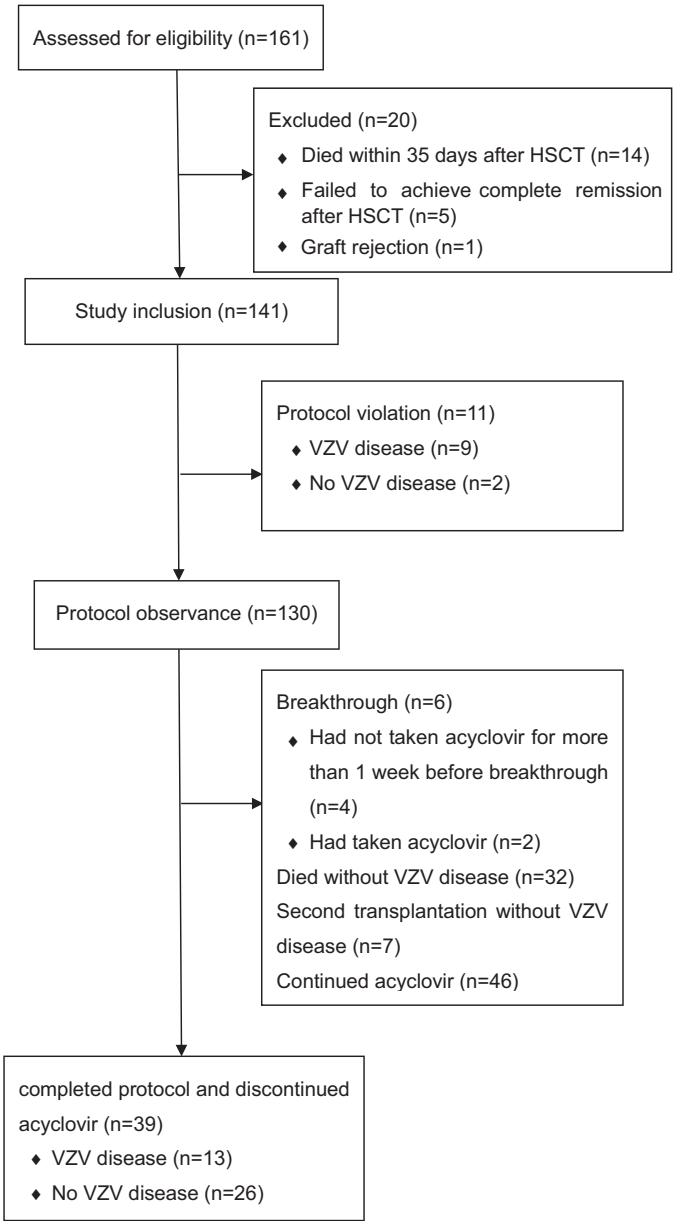

Figure 1. Flow diagram of 161 registered patients.

Table 1
Patient characteristics

Characteristics	
Median age, years (range)	45 (15–65)
Sex, *n* (%)	
Male	83 (58.9%)
Female	58 (41.1%)
Disease, *n* (%)	
AML	67 (47.5%)
ALL	14 (9.9%)
MPAL	2 (1.4%)
CML	3 (2.1%)
MDS	16 (11.4%)
NHL/ATL	23 (16.3%)
SAA	12 (8.5%)
Others	4 (2.8%)
Disease risk, *n* (%)	
Standard	111 (78.7%)
High	30 (21.3%)
Donor, *n* (%)	
Related	56 (39.7%)
Unrelated	85 (60.3%)
HLA (antigen) compatibility, *n* (%)[a]	
Matched	107 (75.9%)
Mismatched	34 (24.1%)
HLA (allele) compatibility, *n* (%)[a]	
Matched	81 (57.5%)
Mismatched	48 (34.0%)
Uncertain/missing	12 (8.5%)
Graft source, *n* (%)	
Bone marrow	73 (58.9%)
Peripheral blood	47 (33.3%)
Cord blood	11 (7.8%)
Conditioning regimen, *n* (%)	
Myeloablative	81 (57.4%)
Reduced-intensity	60 (42.6%)
GVHD prophylaxis, *n* (%)	
Cyclosporine-based	126 (89.4%)
Tacrolimus-based	15 (10.6%)
Use of ATG/alemtuzumab, *n* (%)	
Yes	19 (13.5%)
No	122 (86.5%)
Acute GVHD, *n* (%)	
Grade 0–I	90 (63.8%)
Grade II–IV	51 (36.2%)
Acute GVHD, *n* (%)	
Grade 0–II	124 (87.9%)
Grade III–IV	17 (12.1%)
Chronic GVHD, *n* (%)	
Extensive	38 (26.9%)
Limited	21 (14.9%)
None	73 (51.8%)
Not evaluable	9 (6.4%)
VZV seropositivity, *n* (%)	
Positive	135 (95.7%)
Negative	1 (0.7%)
Not examined	5 (3.6%)

AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MPAL, mixed phenotype acute leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; ATL, adult T-cell leukemia/lymphoma; SAA, severe aplastic anemia; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; ATG, antithymocyte globulin; VZV, varicella zoster virus.

[a] HLA compatibility was defined according to HLA-A, HLA-B, and HLA-DR loci.

single-center retrospective analysis was approved by the Institutional Review Board of Saitama Medical Center, Jichi Medical University.

2.2. Transplantation procedure

The myeloablative conditioning regimen was mainly a combination of cyclophosphamide (60 mg/kg for 2 days) with either total body irradiation (TBI; 2 Gy twice daily for 3 days) or busulfan (3.2 mg/kg/day for 4 days). The reduced-intensity conditioning regimen was a combination of fludarabine with either busulfan or melphalan, with or without low-dose TBI, for elderly or clinically infirm patients. The conditioning regimen for severe aplastic anemia was a combination of fludarabine, cyclophosphamide, and anti-thymoglobulin, with or without TBI at 2 Gy. Alemtuzumab or anti-thymoglobulin was added for patients who received a haploidentical HSCT.[15]

Prophylaxis for graft-versus-host disease (GVHD) consisted of cyclosporine or tacrolimus combined with short-term methotrexate (10–15 mg/m^2 on day 1, 7–10 mg/m^2 on days 3 and 6, and an optional dose on day 11). The target blood concentration of calcineurin inhibitors was determined based on the disease risk. Standard-risk diseases included acute leukemia in complete remission, chronic myelogenous leukemia in the chronic phase, myelodysplastic syndrome without leukemic transformation, lymphoma in remission, and non-malignant disorders such as aplastic anemia, while more advanced diseases were considered high-risk diseases. Acute GVHD was graded as previously described.[16] Methylprednisolone or prednisolone at 1 mg/kg was added for patients who developed grade II–IV acute GVHD.

Prophylaxis against bacterial, fungal, and *Pneumocystis jirovecii* infection consisted of fluoroquinolones, fluconazole or itraconazole, and sulfamethoxazole/trimethoprim or inhalation of pentamidine, respectively. Pre-emptive therapy with ganciclovir or valganciclovir for cytomegalovirus (CMV) infection was performed by monitoring CMV antigenemia by the C10/11 method weekly after engraftment. The initial doses of ganciclovir and valganciclovir were 5 mg/kg and 900 mg once daily, respectively.[17] When increasing antigenemia was observed, the doses were elevated to 5 mg/kg and 900 mg twice daily, respectively.

2.3. Prophylactic administration of acyclovir

As prophylaxis against herpes simplex virus (HSV) infection, patients treated before August 2009 received oral acyclovir at 200 mg five times daily (ACV1000) from day −7 to 35, whereas patients treated after September 2009 received oral acyclovir at 200 mg once daily (ACV200).[18] When patients could not take acyclovir orally, intravenous acyclovir at 250 mg once and twice daily was administered instead of oral acyclovir in the ACV200 and ACV1000 groups, respectively. In both groups, oral acyclovir was principally continued at 200 mg once daily from day 36 to the end of immunosuppressive therapy and for at least 1 year after HSCT to prevent VZV disease. In the case of CMV infection or disease, acyclovir was discontinued, while ganciclovir, valganciclovir, or foscarnet was used for treatment.

2.4. Diagnosis and treatment of VZV disease

The diagnosis of VZV disease was made based on the presence of characteristic vesicular skin lesions on an erythematous base within a dermatome, or a generalized cutaneous distribution. Microbiological, pathological, and/or serological confirmation was not performed routinely except in equivocal cases. Post-herpetic neuralgia was defined as dermatomal pain persisting beyond 1 month after the initial presentation of VZV disease. VZV disease was treated with oral valacyclovir at 3000 mg/day, oral famciclovir at 1500 mg/day, oral acyclovir at 4000 mg/day, or intravenous acyclovir at 15–30 mg/kg/day for 7 days. In patients with renal impairment, the doses of these drugs were adjusted according to the creatinine clearance.

2.5. Statistical analysis

The cumulative incidence of VZV disease and the impact of possible confounding factors on VZV disease were evaluated using

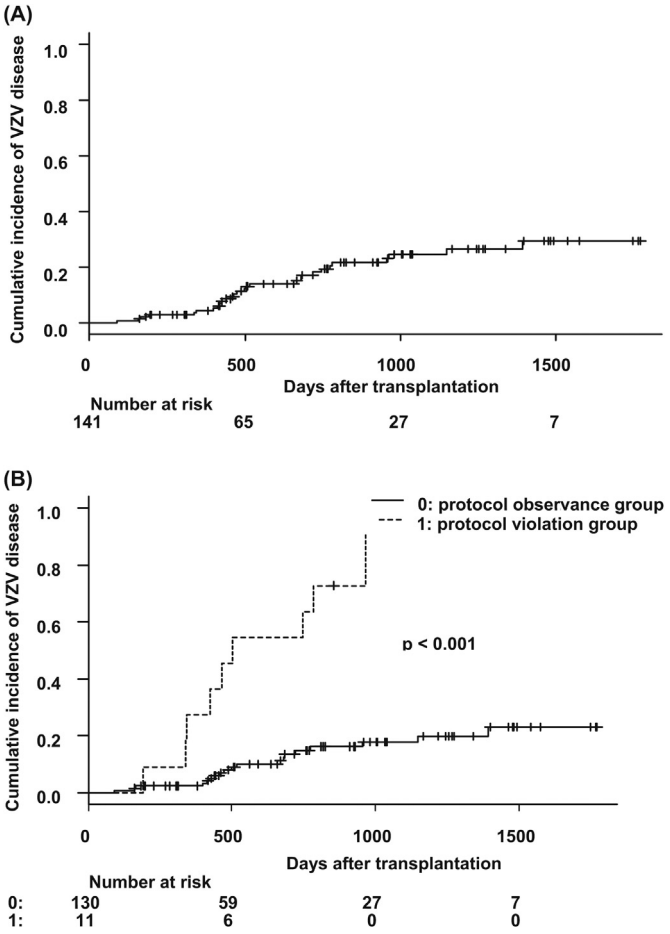

Figure 2. (A) Cumulative incidence of VZV disease after allogeneic HSCT in 141 patients who received acyclovir at 200 mg/day. (B) Cumulative incidence of VZV disease after allogeneic HSCT in 130 patients in the protocol observance group versus 11 patients in the protocol violation group.

Gray's method, while considering death without VZV disease and second transplantation as competing risks.[19] Multivariate analyses for cumulative incidences were performed using Cox proportional hazards regression modeling and Fine and Gray regression modeling.[20] In a multivariate analysis to identify risk factors predictive for VZV disease, variables subjected to the model were selected in a stepwise manner based on Akaike's information criterion (AIC). *p*-Values of less than 0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University),[21] which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6–3) that was designed to add statistical functions that are frequently used in biostatistics.

3. Results

3.1. Administration of prophylactic acyclovir

It was planned to administer oral acyclovir until the end of immunosuppressive therapy and for at least 1 year after HSCT to prevent VZV disease. However, acyclovir was prematurely discontinued in 11 patients – at the request of the patient in two cases, at the physician's discretion in seven, and for reasons that are unclear in two. These patients were regarded as the 'protocol violation group'.

3.2. Incidence and risk factors for VZV disease after HSCT

Overall, 28 of the 141 patients developed VZV disease at a median of 486 days (range 90–1393 days) after HSCT. The cumulative incidence of VZV disease after HSCT was 4.5% (95% confidence interval (CI) 1.8–8.9%) at 1 year and 18.3% (95% CI 11.8–26.0%) at 2 years (Figure 2A). Six patients experienced breakthrough VZV disease during long-term acyclovir, at days 90, 159, 165, 398, 420, and 459 after HSCT. However, four of these six

Table 2
Risk factors for VZV disease after HSCT

Univariate analysis				
Factors	Subgroup	*n*	Incidence at 3 years, % (95% CI)	*p*-Value
Age	<45 years	70	23.5 (13.1–35.7)	0.88
	≥45 years	71	25.6 (14.1–38.7)	
Sex	Male	83	20.8 (11.3–32.2)	0.56
	Female	58	29.7 (16.7–44.0)	
Disease	AML	67	20.9 (10.4–33.8)	0.96
	ALL	14	29.9 (5.1–61.2)	
	MPAL	2	NA[a]	
	CML	3	33.3 (0.1–83.2)	
	MDS	16	15.5 (2.2–40.4)	
	NHL/ATL	23	29.6 (11.2–50.8)	
	SAA	12	34.4 (6.5–65.9)	
	Others	4	25.0 (0.3–71.4)	
Disease risk	Standard	111	19.7 (11.8–28.9)	0.13
	High	30	42.6 (20.2–63.5)	
Conditioning regimen	Myeloablative	81	23.7 (13.8–35.1)	0.80
	Reduced-intensity	60	26.6 (13.7–41.4)	
Donor	Related	56	15.4 (6.6–27.6)	0.11
	Unrelated	85	32.1 (20.0–44.8)	
HLA (antigen) compatibility[b]	Matched	107	25.5 (16.3–35.6)	0.58
	Mismatched	34	21.6 (7.2–40.9)	
HLA (allele) compatibility[b]	Matched	81	24.0 (14.3–35.2)	0.92
	Mismatched	48	25.5 (9.5–45.3)	
	Uncertain/missing	12	27.8 (4.8–58.3)	
Graft source	Bone marrow	83	29.5 (18.6–41.3)	0.24
	Peripheral blood	47	13.6 (4.7–27.1)	
	Cord blood	11	NA[c]	
GVHD prophylaxis	Cyclosporine-based	126	23.4 (15.1–32.7)	0.16
	Tacrolimus-based	15	38.9 (9.4–68.5)	
Use of ATG/alemtuzumab	Yes	19	30.3 (8.6–56.0)	0.66
	No	122	23.8 (15.4–33.3)	
Protocol violation	Yes	11	NA[d]	<0.001
	No	130	17.7 (10.7–26.3)	

Multivariate analysis			
Factor	Hazard ratio	95% CI	*p*-Value
Protocol violation	7.50	3.60–15.63	<0.001

VZV, varicella zoster virus; HSCT, hematopoietic stem cell transplantation; CI, confidence interval; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MPAL, mixed phenotype acute leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; ATL, adult T-cell leukemia/lymphoma; SAA, severe aplastic anemia; NA, not available; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; ATG, antithymocyte globulin.

[a] The cumulative incidence of VZV disease after transplantation was 0.0% (0.0–0.0%) at 225 days.

[b] HLA compatibility was defined according to HLA-A, HLA-B, and HLA-DR loci.

[c] The cumulative incidence of VZV disease after transplantation was 46.8% (0.4–90.2%) at 929 days.

[d] The cumulative incidence of VZV disease after transplantation was 90.9% (0.0–99.9%) at 964 days.

Table 3
Multivariate analysis treating the use of acyclovir as a time-dependent covariate, excluding patients with protocol violation

Factor	Hazard ratio	95% CI	*p*-Value
Age ≥45 years	1.18	0.33–4.25	0.80
Sex: female	1.96	0.70–5.45	0.20
Disease risk: high	2.30	0.71–7.41	0.16
Conditioning regimen: reduced-intensity	1.02	0.28–3.77	0.97
Donor: unrelated	0.89	0.16–5.16	0.90
HLA (antigen) compatibility: mismatched	0.53	0.054–5.23	0.59
Graft source: peripheral blood	0.44	0.064–3.02	0.40
Graft source: cord blood	1.40	0.090–21.54	0.81
GVHD prophylaxis: cyclosporine-based	0.69	0.14–3.44	0.65
Use of ATG/alemtuzumab	1.37	0.097–19.16	0.82
Discontinuation of acyclovir	5.90	1.56–22.37	<0.001

CI, confidence interval; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; ATG, antithymocyte globulin.

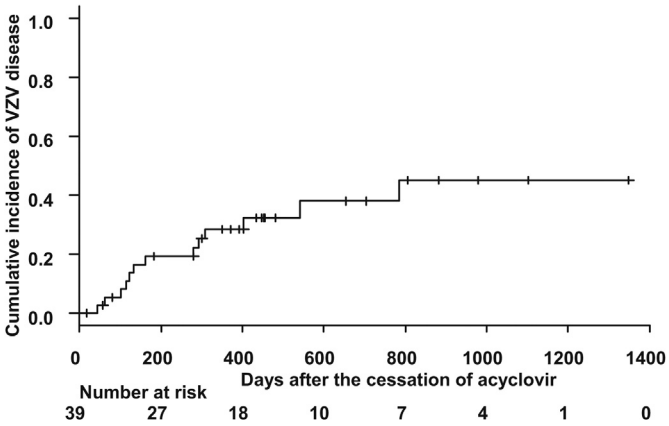

Figure 3. Cumulative incidence of VZV disease after the cessation of long-term acyclovir in 39 patients.

patients had not taken acyclovir for more than 1 week before breakthrough VZV disease due to poor compliance. The six patients developed VZV disease in a limited dermatomal distribution and responded promptly to a therapeutic dose of valacyclovir. In the multivariate analysis of the whole population, protocol violation was the only independent significant factor that increased the incidence of VZV disease (hazard ratio (HR) 7.50, 95% CI 3.60–15.63, $p < 0.001$, Table 2, Figure 2B). Nine of the 11 patients who were included in the protocol violation group developed VZV disease at a median of 464 days (range 191–964 days) after HSCT. The cumulative incidence of VZV disease at 1 year and 2 years after HSCT was 27.3% (95% CI 5.8–55.2%) and 54.5% (95% CI 20.6–79.2%), respectively, in the protocol violation group, and 2.3% (95% CI 0.6–6.1%) and 14.8% (95% CI 8.6–22.6%), respectively, in the protocol observance group ($p < 0.001$, Figure 2B). Next, we performed an analysis treating the use of acyclovir as a time-dependent covariate, excluding patients with protocol violation. The discontinuation of acyclovir was the only significant factor for the development of VZV disease (HR 5.90, 95% CI 1.56–22.37, $p < 0.001$, Table 3).

Table 4
Risk factors for VZV disease after the cessation of acyclovir

Univariate analysis				
Factors	Subgroup	*n*	Incidence at 2 years, % (95% CI)	*p*-Value
Age	<40 years	20	12.9 (1.9–34.6)	0.0066
	≥40 years	19	63.5 (26.2–85.7)	
Sex	Male	22	25.2 (8.8–45.9)	0.32
	Female	17	56.5 (16.9–83.3)	
Disease risk	Standard	32	31.3 (13.2–51.5)	0.28
	High	7	67.9 (9.8–93.7)	
Conditioning regimen	Myeloablative	27	36.3 (15.7–57.5)	0.86
	Reduced-intensity	12	37.9 (10.0–66.4)	
Donor	Related	17	21.1 (4.6–45.7)	0.14
	Unrelated	22	51.4 (21.8–74.8)	
HLA (antigen) compatibility[a]	Matched	32	37.5 (18.8–56.3)	0.96
	Mismatched	7	NA[b]	
HLA (allele) compatibility[a]	Matched	25	32.6 (17.8–55.0)	0.47
	Mismatched	9	NA[c]	
	Uncertain/missing	5	20.0 (0.4–63.2)	
Graft source	Bone marrow	23	45.0 (21.4–66.1)	0.62
	Peripheral blood	13	21.1 (2.5–51.7)	
	Cord blood	3	NA[d]	
GVHD prophylaxis	Cyclosporine-based	35	36.2 (17.8–55.0)	0.26
	Tacrolimus-based	4	NA[e]	
Duration of ACV prophylaxis	<1.5 years	28	44.9 (21.8–65.6)	0.26
	≥1.5 years	11	20.0 (2.6–49.0)	
Lymphocyte count at the cessation of ACV	$<2 \times 10^9$/l	25	34.9 (15.9–54.7)	0.71
	$\geq 2 \times 10^9$/l	14	45.6 (7.3–79.0)	
Chronic GVHD	Yes	17	48.1 (13.3–76.7)	0.71
	No	22	32.2 (12.2–54.4)	
Duration of ACV prophylaxis after the cessation of immunosuppressive drugs	<100 days	18	43.1 (15.3–68.6)	0.75
	≥100 days	21	34.0 (11.2–58.8)	

VZV, varicella zoster virus; HLA, human leukocyte antigen; NA, not available; GVHD, graft-versus-host disease; ACV, acyclovir; CI, confidence interval.
[a] HLA compatibility was defined according to HLA-A, HLA-B, and HLA-DR loci.
[b] The cumulative incidence of VZV disease after the cessation of acyclovir was 31.4% (3.0–68.3%) at 455 days.
[c] The cumulative incidence of VZV disease after the cessation of acyclovir was 35.2% (6.7–66.8%) at 455 days.
[d] The cumulative incidence of VZV disease after the cessation of acyclovir was 50.0% (0.0–96.0%) at 350 days.
[e] The cumulative incidence of VZV disease after the cessation of acyclovir was 50.0% (2.3–88.1%) at 482 days.

Table 5
Clinical outcomes of VZV disease (n = 28)

Localized zoster, *n* (%)	26 (93%)
Trigeminal	4
Cervical	6
Thoracic	10
Lumbar	2
Sacral	4
Disseminated disease, *n* (%)	2 (7%)
Cutaneous	2
Visceral	1[a]
Meningoencephalitis	1[b]
Hospitalized, *n* (%)	
Yes	2 (7%)
No	26 (93%)
Treatment, *n* (%)	
Acyclovir IV	1 (3.5%)
Acyclovir PO	1 (3.5%)
Valacyclovir	24 (86%)
Famciclovir	1 (3.5%)
No treatment	1 (3.5%)
Complications, *n* (%)	
Post-herpetic neuralgia	8 (29%)
Facial paralysis	1 (3.5%)
Neurologic symptoms	1 (3.5%)[c]
None	18 (64%)

VZV, varicella zoster virus; IV, intravenous; PO, by mouth.
[a] One patient had both disseminated cutaneous zoster and visceral involvement.
[b] One patient had both disseminated cutaneous zoster and meningoencephalitis.
[c] Neurologic symptoms, including paralysis in the left lower extremity, pain in both legs, and rectal/bladder disorder, persisted in one patient who developed VZV meningoencephalitis.

3.3. Incidence and risk factors for VZV disease after the cessation of acyclovir

Of the 141 patients who received long-term acyclovir, 50 discontinued acyclovir before the onset of VZV disease, death, or second transplantation. We analyzed the incidence and risk factors for VZV disease after the cessation of acyclovir in 39 of the 50 patients without protocol violation (Figure 1). The median duration of acyclovir prophylaxis was 400 days (range 364–1230 days) and the median follow-up duration after the cessation of acyclovir was 370 days (range 17–1347 days). Thirteen of the 39 patients developed VZV disease at a median of 163 days (range 44–784 days) after the discontinuation of acyclovir. The cumulative incidence of VZV disease after the cessation of acyclovir was 28.4% (95% CI 14.6–44.0%) at 1 year and 38.0% (95% CI 20.1–55.8%) at 2 years (Figure 3). In a univariate analysis, only age ≥40 years was significantly associated with a higher incidence of VZV disease (Table 4).

3.4. Clinical outcomes of VZV disease after HSCT

Twenty-six of the 28 patients developed VZV disease in a localized dermatomal distribution (Table 5). Localized zoster could be treated successfully with oral antiviral agents without hospitalization. The other two patients developed cutaneous disseminated VZV disease at days 464 and 681 after HSCT and were hospitalized for treatment. One of the two patients developed VZV meningoencephalitis at 115 days after the cessation of acyclovir and was treated with intravenous acyclovir at 30 mg/kg/day.[22] The other patient had abdominal pain with cutaneous disseminated VZV disease at 112 days after the cessation of acyclovir, and we considered it to be a symptom of visceral involvement. Although no patient died directly of VZV disease, complications after VZV disease were observed in 10 patients. Neurologic symptoms, including paralysis in the left lower extremity, pain in both legs, and a rectal/bladder disorder, persisted in one patient who developed VZV meningoencephalitis, while eight patients developed post-herpetic neuralgia and the other developed unilateral facial paralysis (Ramsay Hunt syndrome).

4. Discussion

This study demonstrated that the use of acyclovir at 200 mg/day was associated with a low incidence of VZV disease after allogeneic HSCT. On the other hand, a small number of patients experienced breakthrough VZV disease during long-term acyclovir and approximately 40% of patients developed VZV disease after the discontinuation of acyclovir. In particular, patients who had not taken acyclovir regularly due to poor compliance and who violated the protocol more frequently developed VZV disease, although we planned to administer oral acyclovir until the end of immunosuppressive therapy and for at least 1 year after HSCT. The cumulative incidence of VZV disease after HSCT was significantly higher in the protocol violation group than in the protocol observance group. These results suggest that the long-term administration of acyclovir based on our protocol was highly effective for preventing VZV disease.

However, the development of VZV disease after the cessation of long-term acyclovir remains unresolved. In a univariate analysis, only age ≥40 years was significantly associated with a higher incidence of VZV disease. However, this result might be somewhat incidental. There was only one patient who restarted immunosuppressive agents, and therefore we could not analyze the effect of the resumption of immunosuppressive therapy. Among previous studies, Erard et al. demonstrated that late-onset VZV disease was further decreased by extended prophylaxis beyond 1 year in patients who remained on immunosuppressive drugs.[10] The finding of the current study – that protocol violation was significantly associated with a higher incidence of VZV disease – is consistent with their conclusion. We cannot, however, ignore the possibility that the increased incidence of VZV disease in protocol violators was not because of the acyclovir discontinuation but because acyclovir tended to be more frequently discontinued in patients who were at higher risk for VZV disease. However, this is less likely, since the major reason for protocol violation was physician discretion, not based on the physical status of the patient. Therefore, acyclovir prophylaxis should be continued for at least as long as the immunosuppressive drugs are administered. However, the development of VZV disease after the discontinuation of acyclovir cannot be eliminated even by this strategy, and immune reconstitution against VZV may be a more important issue. Boeckh et al. demonstrated that there was no statistically significant difference in the reconstitution of VZV-specific T-cell responses between patients who received acyclovir at 800 mg twice daily and those who received placebo.[8] This finding suggests that subclinical VZV reactivation continues to occur during prophylaxis and that this antigen exposure may boost immunity and prevent subsequent symptomatic VZV disease.[23,24] However, additional strategies are required, since the natural reconstitution of VZV-specific T-cell immunity after allogeneic HSCT was not sufficient to eradicate VZV disease. A possible strategy is to administer VZV vaccine. Hata et al. demonstrated that inactivated varicella vaccine significantly reduced clinical VZV disease in patients who underwent autologous HSCT.[25] Although no data are available on the effectiveness of inactivated varicella vaccine in allogeneic HSCT recipients, several small retrospective studies have reported that the live attenuated varicella vaccine is safe and immunogenic,[26,27] and recent vaccine guidelines permit the use of a live attenuated varicella vaccine in selected patient groups.[28] Prospective studies are necessary to evaluate the safety, efficacy, and immunogenicity of the varicella vaccine.

In this study, the incidence of disseminated VZV disease was only 7% and no patient died directly of VZV disease, as found in

previous studies.[10,12,13] An important benefit of long-term acyclovir prophylaxis may be the prevention of disseminated VZV disease and its complications, although this study was too small to show such a benefit statistically. A delay in the onset of VZV disease by long-term acyclovir prophylaxis allows VZV-specific immune reconstitution, which results in a marked decrease in disseminated VZV disease.

The minimal effective dose of long-term acyclovir also remains unclear. In this study, acyclovir was administered at a dose of 200 mg, which is the minimal dose used in previous studies.[5–8,10,13] This dose was as effective at preventing VZV disease as acyclovir at higher doses in previous studies (600–3200 mg/day), and was superior in terms of low cost and drug compliance, since only one dose was required per day. On the other hand, a major concern regarding long-term ultra-low-dose acyclovir prophylaxis is the emergence of resistant VZV strains. In this study, acyclovir-resistant VZV was not observed, although there were six cases of breakthrough localized zoster that responded well to a therapeutic dose of valacyclovir. About 300 patients, including those in our previous studies, have received long-term ultra-low-dose acyclovir prophylaxis and have not developed clinically resistant VZV disease.[12] In addition, acyclovir-resistant HSV was not observed, as described previously.[18]

In conclusion, this study shows that long-term ultra-low-dose acyclovir appears to be effective for preventing VZV disease, especially disseminated VZV disease, after allogeneic HSCT. The incidence of VZV disease in patients who violated our protocol was extremely high, and therefore we recommend continuing acyclovir until the end of immunosuppressive therapy and for at least 1 year after HSCT. However, additional strategies, such as the combination of long-term acyclovir prophylaxis and the administration of varicella vaccine, may be needed to eradicate VZV disease.

Conflict of interest: The authors declare no conflict of interest or funding.

References

1. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. *J Infect Dis* 1985;**152**:1172–81.
2. Han CS, Miller W, Haake R, Weisdorf D. Varicella zoster infection after bone marrow transplantation: incidence, risk factors and complications. *Bone Marrow Transplant* 1994;**13**:277–83.
3. Arvin AM. Varicella-zoster virus: pathogenesis, immunity, and clinical management in hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant* 2000;**6**:219–30.
4. Koc Y, Miller KB, Schenkein DP, Griffith J, Akhtar M, DesJardin J, et al. Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome. *Biol Blood Marrow Transplant* 2000;**6**:44–9.
5. Ljungman P, Wilczek H, Gahrton G, Gustavsson A, Lundgren G, Lonnqvist B, et al. Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. *Bone Marrow Transplant* 1986;**1**:185–92.
6. Selby PJ, Powles RL, Easton D, Perren TJ, Stolle K, Jameson B, et al. The prophylactic role of intravenous and long-term oral acyclovir after allogeneic bone marrow transplantation. *Br J Cancer* 1989;**59**:434–8.
7. Steer CB, Szer J, Sasadeusz J, Matthews JP, Beresford JA, Grigg A. Varicella-zoster infection after allogeneic bone marrow transplantation: incidence, risk factors and prevention with low-dose aciclovir and ganciclovir. *Bone Marrow Transplant* 2000;**25**:657–64.
8. Boeckh M, Kim HW, Flowers ME, Meyers JD, Bowden RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation—a randomized double-blind placebo-controlled study. *Blood* 2006;**107**:1800–5.
9. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep* 2000;**49**:1–125. CE1-7.
10. Erard V, Guthrie KA, Varley C, Heugel J, Wald A, Flowers ME, et al. One-year acyclovir prophylaxis for preventing varicella-zoster virus disease after hematopoietic cell transplantation: no evidence of rebound varicella-zoster virus disease after drug discontinuation. *Blood* 2007;**110**:3071–7.
11. Kanda Y, Mineishi S, Saito T, Saito A, Yamada S, Ohnishi M, et al. Long-term low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2001;**28**:689–92.
12. Asano-Mori Y, Kanda Y, Oshima K, Kako S, Shinohara A, Nakasone H, et al. Long-term ultra-low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. *Am J Hematol* 2008;**83**:472–6.
13. Thomson KJ, Hart DP, Banerjee L, Ward KN, Peggs KS, Mackinnon S. The effect of low-dose aciclovir on reactivation of varicella zoster virus after allogeneic haemopoietic stem cell transplantation. *Bone Marrow Transplant* 2005;**35**:1065–9.
14. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Bone Marrow Transplant* 2009;**44**:453–558.
15. Kanda Y, Oshima K, Kako S, Fukuda T, Uchida N, Miyamura K, et al. In vivo T-cell depletion with alemtuzumab in allogeneic hematopoietic stem cell transplantation: combined results of two studies on aplastic anemia and HLA-mismatched haploidentical transplantation. *Am J Hematol* 2013;**88**:294–300.
16. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995;**15**:825–8.
17. Kanda Y, Mineishi S, Saito T, Saito A, Ohnishi M, Niiya H, et al. Response-oriented preemptive therapy against cytomegalovirus disease with low-dose ganciclovir: a prospective evaluation. *Transplantation* 2002;**73**:568–72.
18. Kawamura K, Wada H, Yamasaki R, Ishihara Y, Sakamoto K, Ashizawa M, et al. Low-dose acyclovir prophylaxis for the prevention of herpes simplex virus disease after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis* 2013;**15**:457–65.
19. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;**18**:695–706.
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509.
21. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013;**48**:452–8.
22. Suzuki J, Ashizawa M, Okuda S, Wada H, Sakamoto K, Terasako K, et al. Varicella zoster virus meningoencephalitis after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis* 2012;**14**:E7–12.
23. Wilson A, Sharp M, Koropchak CM, Ting SF, Arvin AM. Subclinical varicella-zoster virus viremia, herpes zoster, and T lymphocyte immunity to varicella-zoster viral antigens after bone marrow transplantation. *J Infect Dis* 1992;**165**:119–26.
24. Merindol N, Salem Fourati I, Brito RM, Grenier AJ, Charrier E, Cordeiro P, et al. Reconstitution of protective immune responses against cytomegalovirus and varicella zoster virus does not require disease development in pediatric recipients of umbilical cord blood transplantation. *J Immunol* 2012;**189**:5016–28.
25. Hata A, Asanuma H, Rinki M, Sharp M, Wong RM, Blume K, et al. Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. *N Engl J Med* 2002;**347**:26–34.
26. Kussmaul SC, Horn BN, Dvorak CC, Abramovitz L, Cowan MJ, Weintrub PS. Safety of the live, attenuated varicella vaccine in pediatric recipients of hematopoietic SCTs. *Bone Marrow Transplant* 2010;**45**:1602–6.
27. Chou JF, Kernan NA, Prockop S, Heller G, Scaradavou A, Kobos R, et al. Safety and immunogenicity of the live attenuated varicella vaccine following T replete or T cell-depleted related and unrelated allogeneic hematopoietic cell transplantation (alloHCT). *Biol Blood Marrow Transplant* 2011;**17**:1708–13.
28. Ljungman P, Cordonnier C, Einsele H, Englund J, Machado CM, Storek J, et al. Vaccination of hematopoietic cell transplant recipients. *Bone Marrow Transplant* 2009;**44**:521–6.